Synthesis and kinase inhibitory potencies of new pyrido[3,4-*g*]quinazolines substituted at the 8-position

Yannick J. Esvan,[a] Béatrice Josselin,[b] Blandine Baratte,[b] Stéphane Bach,[b] Sandrine Ruchaud,[b] Fabrice Anizon,[a] Francis Giraud,*[a,] and Pascale Moreau*[a]

[a] *Université Clermont Auvergne, CNRS, SIGMA Clermont, ICCF, F-63000 Clermont-Ferrand, France*
[b] *Sorbonne Université, CNRS, Plateforme de Criblage KISSf (Kinase Inhibitor Specialized Screening Facility), FR2424, Station Biologique, Place Georges Teissier, F-29688 Roscoff, France*
Email: *francis.giraud@uca.fr; pascale.moreau@uca.fr*

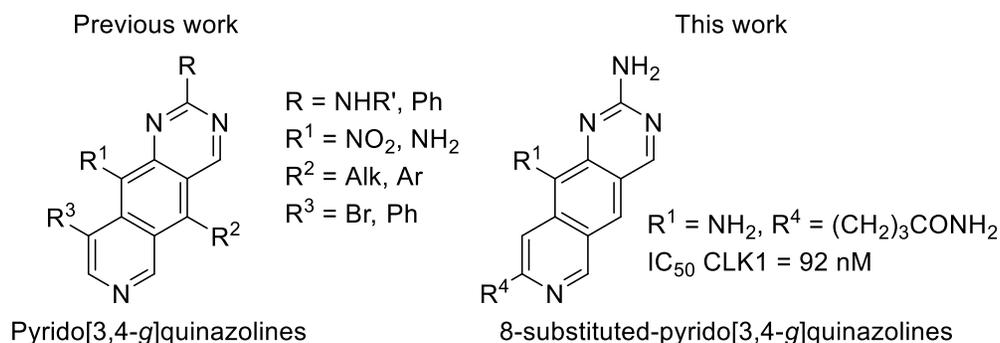*Dedicated to Jan Bergman on the occasion of his 80th birthday*

Abstract

As part of the structure-activity relationship study undertaken around the pyrido[3,4-*g*]quinazoline moiety, new derivatives substituted at the 8-position were synthesized and evaluated regarding their ability to inhibit various protein kinases (CDK5, CLK1, DYRK1A, CK1, GSK3). Most active compound exhibited a nanomolar potency toward CLK1, demonstrating that substitution at 8-position is compatible with CLK1 inhibition.

Previous work

R = NHR', Ph
R^1 = NO_2, NH_2
R^2 = Alk, Ar
R^3 = Br, Ph

Pyrido[3,4-*g*]quinazolines

This work

R^1 = NH_2, R^4 = $(CH_2)_3CONH_2$
IC_{50} CLK1 = 92 nM

8-substituted-pyrido[3,4-*g*]quinazolines

Keywords: Fused azines, isoquinolines, pyrimidines, pyridoquinazolines

Introduction

A few years ago, as part of our program dedicated to the identification of new heteroaromatic compounds with kinase inhibitory potencies, we designed and synthesized a new pyrido[3,4-*g*]quinazoline series for the inhibition of CDC-like kinase 1 (CLK1)/Dual specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A).[1] The structure-activity relationship (SAR) studies undertaken around this new series (Figure 1) showed that the kinase inhibition profile was highly dependent on the scaffold substitution. For example, while analogues diversely substituted at 2- and 10-positions were active toward CLK1/DYRK1A, the introduction of alkyl/aryl groups at the 5-position was detrimental to the inhibition of CLK1/DYRK1A in favour of the one of CDK5/GSK3.[1-4] To complete this SAR study, we decided to focus our interest on the 8-position of the pyridoquinazoline scaffold (Figure 1), evaluating the impact of this structural modification on the biological activities.
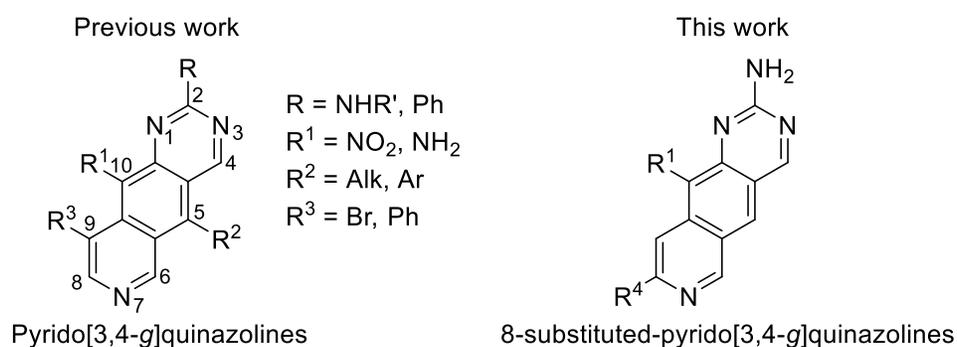

Figure 1. Structural modifications performed in the pyrido[3,4-*g*]quinazoline series as part of our structure-activity relationship study.

As previously reported,[1-4] the synthetic pathway was based on the preparation of a tetrasubstituted benzene derivative **A**, with substituents at the 1- and 2-positions used to construct the isoquinoline moiety (after Sonogashira cross-coupling with TMS-acetylene and subsequent cyclization in the presence of ammonia), while those at the 4- and 5-positions allowed the formation of the aminopyrimidine moiety (after oxidation, nitration and condensation with diversely substituted guanidine/amidine derivatives) (Scheme 1).
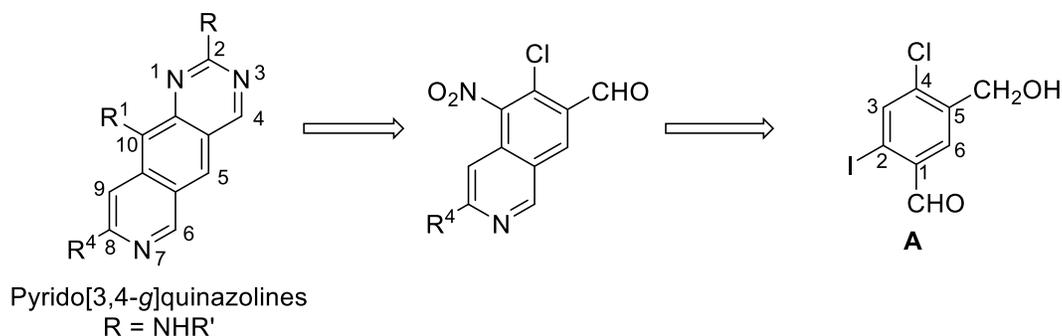

Scheme 1. Synthetic strategy used to prepare the pyrido[3,4-*g*]quinazoline tricyclic scaffold.

To generate a new compound library, the functionalization of the 8-position was achieved *via* a similar approach using, in the Sonogashira coupling step, various alkynes bearing functional groups that could allow post-modifications after the formation of the tricyclic system.

Results and Discussion

Our first idea to prepare pyrido[3,4-*g*]quinazolines bearing aminoalkyl side chains at the 8-position was the use, in the Sonogashira coupling step, of a but-1-yne derivative bearing at the 4-position a phthalimide protected amine precursor. Therefore compound **A** was reacted with 2-(but-3-yn-1-yl)isoindoline-1,3-dione[5] in the presence of PdCl$_2$(PPh$_3$)$_2$, CuI and Et$_3$N in DMF to afford **1** in 73% yield.[6] Compound **1** was then cyclized to the corresponding isoquinoline **2** in the presence of ammonia in methanol[7] before primary alcohol oxidation with MnO$_2$[8], leading to chloroaldehyde **3** (Scheme 2). The next step was the introduction of a nitro group at the 5-position of the isoquinoline moiety in order to allow subsequent formation of the aminopyrimidine moiety. Unfortunately, the nitro derivative was never obtained due to a preferred nitration of the phthalimide moiety.
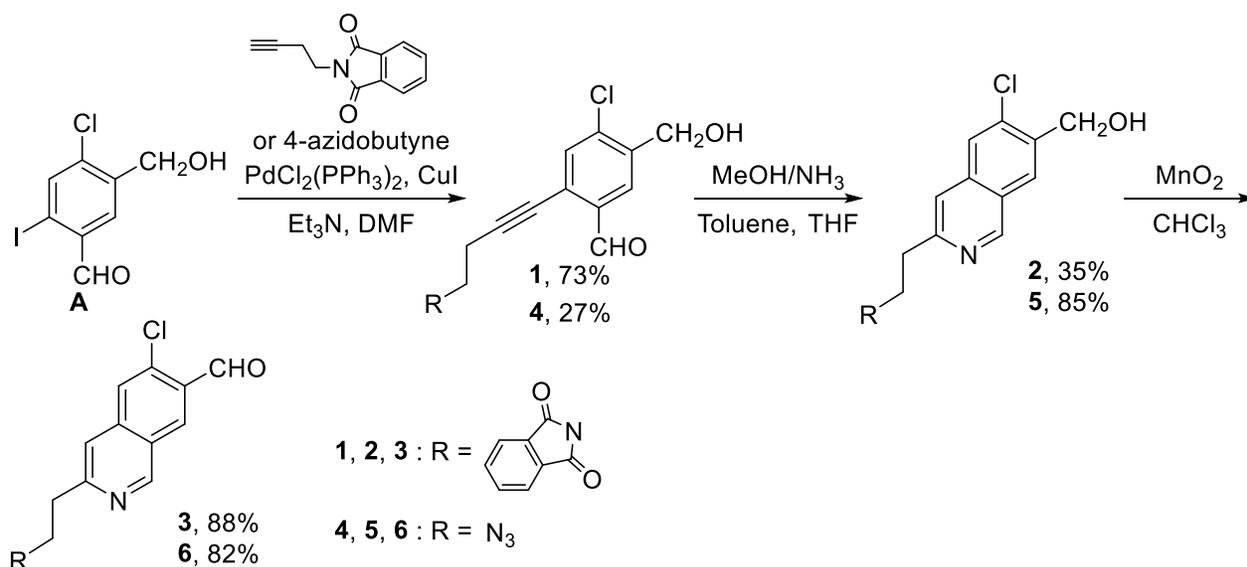

Scheme 2. Phthalimido/azido strategy: synthesis of compounds **3** and **6**.

Thus, we decided to use an azido group as amine precursor. The synthesis of the corresponding isoquinolines **5/6** was performed *via* the same synthetic sequence using 4-azidobut-1-yne[9] as alkyne partner in the first step (Scheme 2). Regrettably, compound **6** was unstable under the nitration conditions used. Formation of the aminopyrimidine ring directly from **3** or **6** in the presence of guanidine carbonate, without activation of the isoquinoline by an electron-withdrawing group, was unsuccessful.

Because of these failures, the preparation of another intermediate, an isoquinoline bearing at the 3-position an ethyl side chain bearing a mesylate terminal group, likely to undergo a nucleophilic displacement with amines, was considered. Therefore, compound **A** primary alcohol was protected as a THP group before Sonogashira coupling in the presence of but-3-yn-1-ol leading to **8** that was cyclized to the corresponding isoquinoline **9** (Scheme 3). Finally, chloroaldehyde **12** was prepared by mesylation of the primary alcohol,

cleavage of the THP group under mild acidic conditions, and oxidation. In this case, the nitration reaction led to the attempted product **13** in 77% yield. In the last step, the formation of the aminopyrimidine moiety performed in the presence of guanidine carbonate, led to tricyclic compound **14**. Basic conditions used also led to an elimination reaction (Scheme 3). Due to low solubility of **14**, all further double bond transformations assayed (hydroboration, hydroamination, oxidative cleavage) were unsuccessful.
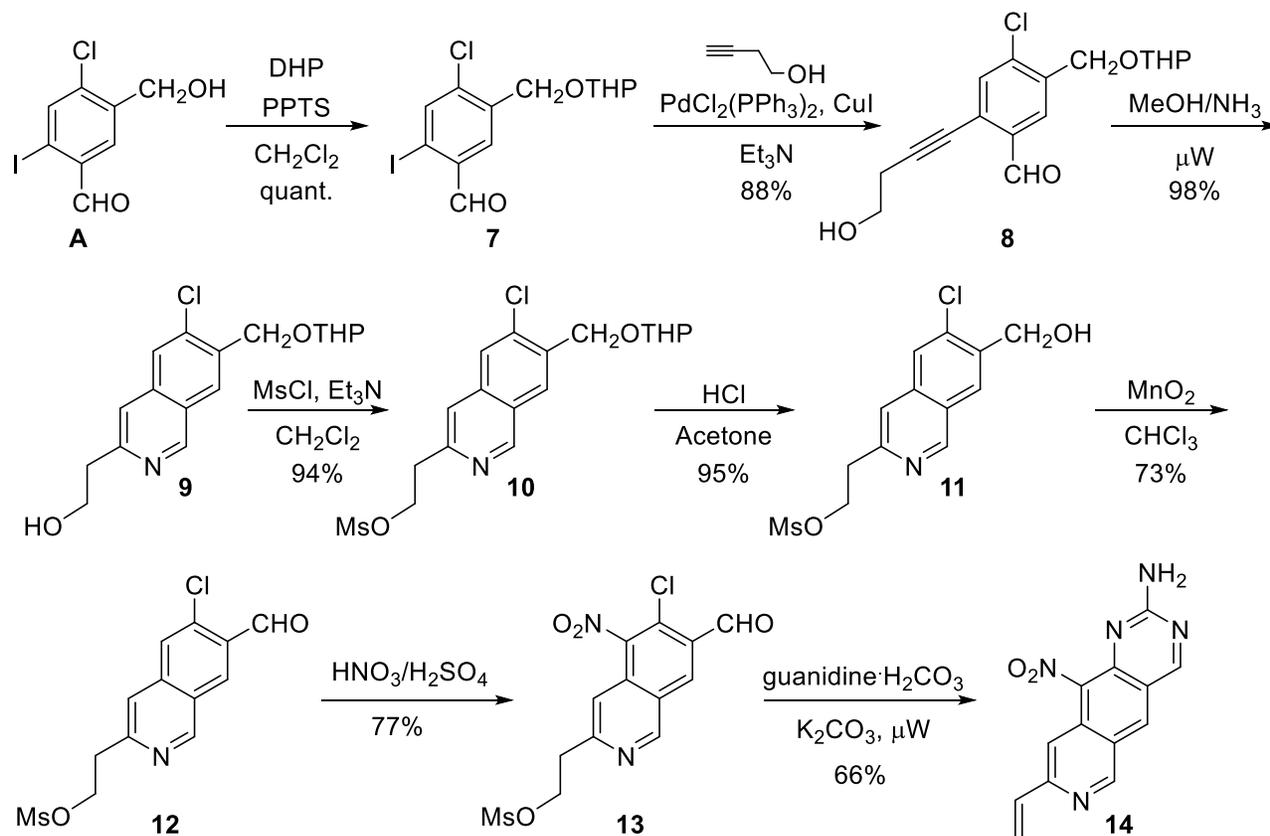
Scheme 3. Mesylate strategy: synthesis of compound **14**.

Another strategy was to introduce a side chain bearing a nitrile group, that could be reduced to the corresponding amino analogue or hydrolyzed to give the corresponding amide. Therefore, compound **A** was reacted with pent-4-ynenitrile under Sonogashira coupling conditions to give **15** that was cyclized to the corresponding isoquinoline **16** in the presence of ammonia in methanol under microwave irradiation before primary alcohol oxidation leading to chloroaldehyde **17** (Scheme 4). Again, next step was the introduction of a nitro group at the 5-position of the isoquinoline moiety. Despite numerous efforts using various nitration conditions (HNO$_3$, Ac$_2$O, AcOH[10] or KNO$_3$, H$_2$SO$_4$/TFA[11] or AgNO$_3$, NBS[12] or HNO$_3$, P$_2$O$_5$/H$_2$SO$_4$-SiO$_2$[13,14] or N$_2$O$_4$[15] or NO$_2$BF$_4$[16] or KNO$_3$/H$_2$SO$_4$[17]), we never managed to prepare intermediate **B**. Instead, nitro analogue **18** exhibiting an amide function was obtained in 85% yield (Scheme 4). However, as compound **18** could lead to new 8-substituted pyrido[3,4-*g*]quinazolines, the synthesis was carried out to give the tricyclic compounds **19** and **20** which were obtained after condensation with guanidine carbonate and subsequent reduction of the nitro group, as already described (Scheme 4).[1]
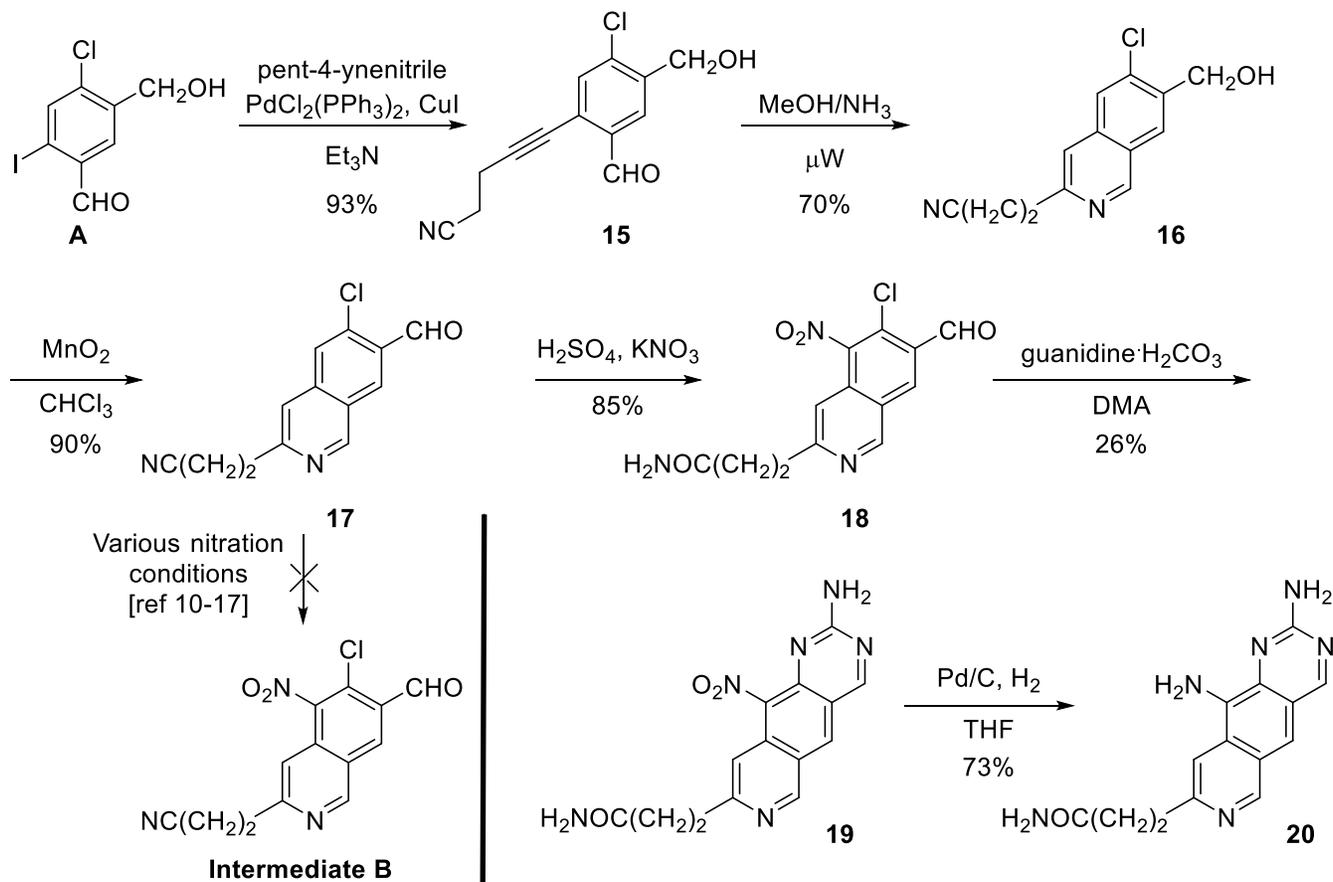
Scheme 4. Nitrile strategy: synthesis of compounds **19** and **20**.

Tricyclic compounds **14**, **19** and **20** were then evaluated toward a small panel of protein kinases (CDK5, CLK1, DYRK1A, CK1 and GSK3) using similar procedures as previously described.[4,18] As shown in Table 1, most active compounds were **14** and **20** with interesting IC_{50} values of 111 nM and 92 nM, respectively, toward CLK1.

Table 1. Kinase inhibition assays (% residual kinase activity)

	CDK5		CLK1		DYRK1A		CK1		GSK3	
	10 μM	1 μM	10 μM	1 μM	10 μM	1 μM	10 μM	1 μM	10 μM	1 μM
14	90	100	17 / 111 nM	33	42	48	62	100	59	85
19	84	100	27	51	67	94	78	94	98	99
20	87	100	14 / 92 nM	25	38	40	74	99	5	77

IC_{50} values were determined when the residual kinase activity was ≤ 35% at a compound concentration of 1 μM. Kinase activities were assayed in triplicate. Typically, the standard deviation of single data points was below 10%. Assays for **19** and **20** were performed using a ^{32}P radioassay in the presence of 15 μM ATP while **14** testing was carried out using the ADP-Glo assay in the presence of 10 μM ATP.

Conclusions

In conclusion, various synthetic strategies were carried out to introduce a functionalized side chain at the 8-position of pyrido[3,4-*g*]quinazoline moiety. The use of the mesylate approach led to vinyl derivative **14** while the nitrile approach allowed the preparation of propionamides **19** and **20**. The evaluation of these new diversely substituted compounds toward five protein kinases showed that compounds **14** and **20** were potent inhibitors of CLK1 with sub-micromolar/nanomolar potencies. Altogether, the results obtained demonstrated that the substitution at the 8-position of this tricyclic heteroaromatic scaffold is compatible with potent kinase inhibition.

Experimental Section

General. Starting materials were obtained from commercial suppliers and used without further purification. Experiments under microwave irradiation were performed using a CEM Discover Benchmate apparatus. IR spectra were recorded on a PerkinElmer spectrum 65 FT-IR spectrometer ($\bar{\nu}$ in cm^{-1}). NMR spectra, performed on a Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz), are reported in ppm using the solvent residual peak as an internal standard; the following abbreviations are used: singlet (s), doublet (d), triplet (t), quadruplet (q), multiplet (m), broad signal (br s). High resolution mass spectra (ESI+) were determined on a high-resolution Waters Micro Q-ToF apparatus (UCA-Partner, Université Clermont Auvergne, Clermont-Ferrand, France). Chromatographic purifications were performed by column chromatography using 40–63 µm silica gel. Reactions were monitored by TLC using fluorescent silica gel plates (60 F254 from Merck). Melting points were measured on a Stuart SMP3 apparatus. The purity of final compound 19 was established to be > 95% by HPLC analysis using a Hitachi liquid chromatograph (Oven 5310, 30 °C; Pump 5160; DAD detector 5430) and a C18 Acclaim column (4.6 mm x 250 mm, 5 µm, 120 Å). Detection wavelength was 240 nm and flow rate 0.5 mL/min. Elution was performed with water / acetonitrile eluent 50/50.

4-Chloro-2-[4-(1,3-dioxoisoindolin-2-yl)but-1-yn-1-yl]-5-(hydroxymethyl)benzaldehyde (**1**). To a solution of A (3.26 g, 11 mmol) in DMF (5 mL), under argon atmosphere, were successively added CuI (230 mg, 1.21 mmol), PdCl$_2$(PPh$_3$)$_2$ (386 mg, 0.55 mmol), Et$_3$N (2.23 mL, 16.5 mmol) and 2-(but-3-yn-1-yl)isoindoline-1,3-dione (2.50 g, 12.54 mmol). The mixture was stirred at 40 °C for 16 h. After cooling, water was added before extraction with EtOAc. Organic layers were dried (MgSO$_4$), filtered, concentrated under reduced pressure and the crude material was purified by flash chromatography using EtOAc/cyclohexane (4:6) yielding compound 1 (2.97 g, 8.07 mmol, 73%) as a yellow solid. TLC R$_f$ = 0.46 (EtOAc/cyclohexane 4:6). ^{1}H NMR (400 MHz, DMSO-d_6) 2.92 (t, *J* 6.8 Hz, 2H), 3.89 (t, *J* 6.4 Hz, 2H), 4.56 (d, *J* 6.0 Hz, 2H), 5.61 (t, *J* 5.6 Hz, 1H), 7.51 (s, 1H), 7.84-7.91 (m, 4H), 7.94 (s, 1H), 10.23 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 18.9, 36.0, 59.8 (CH$_2$), 76.4, 95.3 (C$_{alkyne}$), 123.1 (2 CH$_{pht}$), 126.0, 132.9 (CH$_{arom}$), 134.6 (2 CH$_{pht}$), 125.3, 131.5 (2 C$_{pht}$), 134.1, 136.6, 140.8 (C$_{arom}$), 167.7 (2 CO$_{pht}$), 190.5 (CHO). Mp: 162 – 164 °C. IR (ATR) 3661-2968, 2100 – 2000, 1766, 1702, 1063 cm^{-1}. HRMS (ESI+) calcd for C$_{20}$H$_{15}$^{35}ClNO$_4$ (M+H)$^{+}$ 368.0684, found 368.0692.

2-{2-[6-Chloro-7-(hydroxymethyl)isoquinolin-3-yl]ethyl}isoindoline-1,3-dione (**2**). In a CEM Microwave tube, NH$_3$/MeOH (7N) (4.8 mL) was added to 1 (660 mg, 1.795 mmol). The tube was irradiated at 75 W for 15 min at 130 °C in a microwave oven. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using EtOAc to yield compound 2 (394 mg, 1.074 mmol, 60%) as a beige solid. TLC R$_f$ = 0.34 (EtOAc/cyclohexane 7:3). ^{1}H NMR (400 MHz, DMSO-d_6) 3.18 (t, *J* 7.2 Hz, 2H), 4.00 (t, *J* 6.8 Hz, 2H), 4.70 (d, *J* 6.4 Hz, 2H), 5.61 (t, *J* 5.6 Hz, 1H), 7.65 (s, 1H), 7.83 (m, 4H), 7.99 (s, 1H), 8.19 (s, 1H), 9.24 (s,

1H). ^{13}C NMR (100 MHz, DMSO-d_6) 35.8, 37.7, 60.5 (CH$_2$), 117.5, 123.0 (2 CH$_{pht}$), 125.5, 126.1, 134.3 (2 CH$_{pht}$), 151.8 (CH$_{arom}$), 125.3, 131.6 (2 C$_{pht}$), 134.3, 135.4, 138.6, 152.2 (C$_{arom}$), 167.7 (2 CO$_{pht}$). Mp: 212 – 214 °C. IR (ATR) 3452 – 3250, 2925, 1759, 1696, 1451, 1090 cm^{-1}. HRMS (ESI+) calcd for C$_{20}$H$_{16}$^{35}ClN$_2$O$_3$ (M+H)$^+$ 367.0844, found 367.0833.

6-Chloro-3-[2-(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)ethyl]isoquinolin-7-carbaldehyde (**3**). To a solution of **2** (207.2 mg, 0.565 mmol) in CHCl$_3$ (8 mL) was added MnO$_2$ (147.3 mg, 1.695 mmol). The mixture was stirred at reflux for 18 h with adding of two more equivalents of MnO$_2$ (98.2 mg, 1.129 mmol) after 2 h of reflux. After cooling, filtration of the reaction mixture through a pad of Celite® and washing with EtOAc, the filtrate was concentrated in vacuo. The crude material was triturated with pentane yielding compound **3** (182.4 mg, 0.500 mmol, 88%) after filtration as a beige solid. TLC R$_f$ = 0.48 (EtOAc/cyclohexane 5:5). RMN ^{1}H (400 MHz, DMSO-d_6) 3,23 (t, *J* 7.2 Hz, 2H), 4.02 (t, *J* 6.8 Hz, 2H), 7.77 (s, 1H), 7.83 (m, 4H), 8.15 (s, 1H), 8,72 (s, 1H), 9,45 (s, 1H), 10,40 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 36.0, 37.5 (CH$_2$), 117.8, 123.0 (2 CH$_{pht}$), 127.5, 132.5, 134.4 (2 CH$_{pht}$), 154.1 (CH$_{arom}$), 101.1, 124.6, 130.6, 131.5 (2 C$_{pht}$), 138.5, 155.6 (C$_{arom}$), 167.7 (2 CO$_{pht}$), 189.4 (CHO). Mp: 225 – 227 °C. IR (ATR) 2861, 1761, 1690, 1616, 1452, 1100 cm^{-1} HRMS (ESI+) calcd for C$_{21}$H$_{18}$^{35}ClN$_2$O$_4$ (M+MeOH+H)$^+$ 397.0950, found 397.0941.

2-(4-Azidobut-1-yn-1-yl)-4-chloro-5-(hydroxymethyl)benzaldehyde (**4**). Using standard procedure as described,[1] **A** (1.426 g, 4.81 mmol), CuI (36 mg, 0.192 mmol), PdCl$_2$(PPh$_3$)$_2$ (67 mg, 0.096 mmol), Et$_3$N (20 mL) and 4-azidobutyne (1.143 g, 12.02 mmol) were mixed together and heated at 50 °C overnight. Flash chromatography using CH$_2$Cl$_2$ yielded compound **4** (343 mg, 1.30 mmol, 27%) as a pale yellow powder. TLC R$_f$ = 0.28 (EtOAc/cyclohexane 1:3). ^{1}H NMR (400 MHz, DMSO-d_6) 2.85 (t, *J* 6.4 Hz, 2H), 3.59 (t, *J* 6.4 Hz, 2H), 4.59 (d, *J* 6.0 Hz, 2H), 5.66 (t, *J* 6.0 Hz, 1H), 7.65 (s, 1H), 7.99 (s, 1H), 10.39 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 20.1, 48.9, 59.8 (CH$_2$), 76.4, 95.9 (C$_{alkyne}$), 126.0, 132.9 (CH$_{arom}$), 125.5, 134.3, 136.8, 141.0 (C$_{arom}$), 190.7 (CHO). Mp: 69-70 °C. IR (ATR) 3667-2596, 2106, 1688, 1593, 1459, 1248 cm^{-1}. HRMS (ESI+) calcd for C$_{12}$H$_{11}$^{35}ClN$_3$O$_2$ (M+H)$^+$ 264.0534, found 264.0531.

[3-(2-Azidoethyl)-6-chloroisoquinolin-7-yl]methanol (**5**). Using similar procedure as described for **2**: **4** (325 mg, 1.233 mmol) and NH$_3$/MeOH (3.52 mL, 24.65 mmol) were irradiated at 75 W and 130 °C in a sealed tube for 15 min in a microwave oven. After evaporation of the reaction mixture, flash chromatography using EtOAc/cyclohexane 7:3 to 9:1 yielded compound **5** (277.5 mg, 1.056 mmol, 85%) as a beige solid. TLC R$_f$ = 0.25 (EtOAc/cyclohexane 7:3). ^{1}H NMR (400 MHz, DMSO-d_6) 3.14 (t, *J* 6.4 Hz, 2H), 3.79 (t, *J* 6.4 Hz, 2H), 4.72 (d, *J* 6.4 Hz, 2H), 5.66 (t, *J* 5.2 Hz, 1H), 7.71 (s, 1H), 8.05 (s, 1H), 8.22 (s, 1H), 9.34 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 36.6, 50.0, 60.5 (CH$_2$), 117.8, 125.52, 126.1, 152.02 (CH$_{arom}$), 125.50, 134.5, 135.4, 138.8, 152.00 (C$_{arom}$). Mp: 111-112 °C. IR (ATR) 3524-2439, 2103, 1633, 1593, 1453, 1265 cm^{-1}. HRMS (ESI+) calcd for C$_{12}$H$_{12}$^{35}ClN$_4$O (M+H)$^+$ 263.0694, found 263.0692.

3-(2-Azidoethyl)-6-chloroisoquinoline-7-carbaldehyde (6). Using similar procedure as described for **3**: **5** (275.4 mg, 1.048 mmol) and MnO$_2$ (364 mg, 4.193 mmol) were heated in CHCl$_3$ (10 mL) at reflux for 6 h. 100 mg of MnO$_2$ were added and heating was continued overnight to completion. Filtration of the mixture over Celite pad and washing with EtOAc afforded after evaporation of the filtrate compound **6** (225 mg, 0.865 mmol, 82%) as a yellow powder. TLC R*f* = 0.65 (EtOAc/cyclohexane 1:1). ^{1}H NMR (400 MHz, DMSO-d_6) 3.18 (t, *J* 6.8 Hz, 2H), 3.82 (t, *J* 6.8 Hz, 2H), 7.81 (s, 1H), 8.19 (s, 1H), 8.74 (s, 1H), 9.53 (s, 1H), 10.41 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 36.7, 49.8 (CH$_2$), 118.0, 127.5, 132.5, 154.3 (CH$_{arom}$), 124.7, 130.6, 135.3, 138.5, 155.4 (C$_{arom}$), 189.5 (CHO). Mp: 98-99 °C. IR (ATR) 2082, 1691, 1615, 1445, 1396, 1340, 1291 cm^{-1} HRMS (ESI+) calcd for C$_{12}$H$_{10}$^{35}ClN$_4$O (M+H)$^+$ 261.0538, found 261.0533.

4-Chloro-2-iodo-5-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}benzaldehyde (**7**). Pyridinium *p*-toluenesulfonate (PPTS) (168 mg, 0.668 mmol) and dihydropyrane (DHP) (0.86 mL, 10.1 mmol) were added to a solution of **A** (2

g, 6.76 mmol) in CH_2Cl_2 (36 mL). The reaction mixture was stirred overnight at room temperature before removal of solvent under reduced pressure. Water was added before extraction with EtOAc. Organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure after filtration. The crude material was purified by flash chromatography using EtOAc/cyclohexane (1:6) yielding compound 7 (2.57 g, 6.75 mmol, quant.) as a white solid. TLC R_f = 0.7 (EtOAc/Cyclohexane 1:4). ^{1}H NMR (400 MHz, DMSO-d_6) 1.47-1.73 (m, 6H), 3.41-3.48 (m, 1H), 3.71-3.74 (m, 1H), 4.53 (d, *J* 14.0 Hz, 1H), 4.70 (d, *J* 14.0 Hz, 1H), 4.75 (t, *J* 4.0 Hz, 1H), 7.89 (s, 1H), 8.19 (s, 1H), 9.94 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 18.8, 24.9, 30.0, 61.4, 64.9 (CH_2), 97.9 (CH), 129.7, 140.0 (CH_{arom}), 99.7, 133.9, 137.1, 138.5 (C_{arom}), 194.5 (CHO). Mp: 80–82 °C. IR (ATR) 2936, 1686, 1582, 1450 cm^{-1}. HRMS (ESI+) calcd for $C_{13}H_{15}{}^{35}ClIO_3$ (M+H)$^+$ 402.9568, found 402.9569.

4-Chloro-2-(4-hydroxybut-1-yn-1-yl)-5-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}benzaldehyde (**8**). To a solution of 7 (1.0 g, 2.63 mmol) and but-3-yn-1-ol (0.50 mL, 6.50 mmol) in Et_3N (10 mL), under argon atmosphere, were added $PdCl_2(PPh_3)_2$ (36 mg, 0.052 mmol) and CuI (20 mg, 0.105 mmol). The reaction mixture was heated at 50 °C for 2 h before solvent evaporation under reduced pressure. The crude material was purified by flash chromatography using EtOAc/cyclohexane (1:4 to 1:3) yielding compound 8 (748 mg, 2.32 mmol, 88%) as an orange oil. TLC R_f = 0.25 (EtOAc/cyclohexane 1:4). ^{1}H NMR (400 MHz, DMSO-d_6) 1.49-1.77 (m, 6H), 2.66 (t, *J* 6.6 Hz, 2H), 3.48-3.51 (m, 1H), 3.62 (q, *J* 6.6 Hz, 2H), 3.74-3.80 (m, 1H), 4.59 (d, *J* 14.0 Hz, 1H), 4.75 (d, *J* 14.0 Hz, 1H), 4.78 (t, *J* 3.2 Hz, 1H), 4.98 (t, *J* 6.0 Hz, 1H), 7.71 (s, 1H), 7.92 (s, 1H), 10.38 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 18.9, 23.6, 24.9, 30.0, 59.3, 61.4, 65.0 (CH_2), 97.9 (CH), 127.0, 133.2 (CH_{arom}), 75.0, 97.8 (C), 126.8, 134.2, 136.8, 137.7 (C_{arom}), 190.8 (CHO). IR (ATR) 3433–3400, 2936, 2184, 2256, 1686, 1341 cm^{-1}. HRMS (ESI+) calcd for $C_{17}H_{20}{}^{35}ClO_4$ (M+H)$^+$ 323.1045, found 323.1040.

2-(6-Chloro-7-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}isoquinolin-3-yl)ethan-1-ol (**9**). In a sealed tube, a solution of 8 (181 mg, 0.56 mmol) in 1.6 mL of $MeOH/NH_3$ (7N) was heated at 130 °C for 15 min in a microwave oven (75 W). The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using EtOAc/cyclohexane (90:10 to 100:0 to EtOAc/MeOH 99:1), yielding compound 9 (177 mg, 0.55 mmol, 98%) as an orange solid. TLC R_f = 0.33 (EtOAc/cyclohexane 7:3). ^{1}H NMR (400 MHz, DMSO-d_6) 1.50-1.80 (m, 6 H), 3.01 (t, *J* 6.8 Hz, 2H) 3.50-3.54 (m, 1H), 3.81 (q, *J* 5.6 Hz, 2H), 3.83-3.86 (m, 1H), 4.66 (t, *J* 5.2 Hz, 1H), 4.73 (d, *J* 13.6 Hz, 1H), 4.82 (t, *J* 6 Hz, 1H), 4.87 (d, *J* 13.6 Hz, 1H), 7.64 (s, 1H), 8.07 (s, 1H), 8.19 (s, 1H), 9.31 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 19.0, 25.0, 30.1, 41.1, 60.6, 61.4, 65.8 (CH_2), 97.9 (CH), 117.5, 125.8, 127.6, 151.8 (CH_{arom}), 125.1, 134.4, 134.8, 135.7, 153.8 (C_{arom}). Mp: 102–104 °C. IR (ATR) 3222–2942, 2869, 1685, 1586, 1452, 1212 cm^{-1}. HRMS (ESI$^+$) calcd for $C_{17}H_{21}{}^{35}ClNO_3$ (M+H)$^+$ 322.1205, found 322.1210.

2-(6-Chloro-7-{[(tetrahydro-2*H*-pyran-2-yl)oxy]methyl}isoquinolin-3-yl)ethyl methanesulfonate (**10**). Et_3N (0.52 mL, 3.729 mmol) and methanesulfonyl chloride (0.36 mL, 4.661 mmol) were added slowly to a cooled (0 °C) solution of 9 (1.0 g, 3.107 mmol) in CH_2Cl_2 (1.6 mL). The reaction mixture was stirred at room temperature for 24 h before removal of solvent under reduced pressure. Water was added before extraction with EtOAc. Organic layers were washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure after filtration. The crude material was purified by flash chromatography using EtOAc/cyclohexane (8:2 to 9:1) yielding compound 10 (1.171 g, 2.928 mmol, yield 94 %) as a yellow solid. TLC R_f = 0.45 (EtOAc/cyclohexane 7:3). ^{1}H NMR (400 MHz, DMSO-d_6) 1.46-1.87 (m, 6H), 3.11 (s, 3H), 3.29 (t, *J* 6.4 Hz, 2H), 3.51-3.54 (m, 1H), 3.80-3.84 (m, 1H), 4.65 (t, *J* 6.4 Hz, 2H), 4.70 (d, *J* 13.2 Hz, 1H), 4.83 (t, *J* 6.0 Hz, 1H), 4.89 (d, *J* 13.2 Hz, 1H), 7.73 (s, 1H), 8.10 (s, 1H), 8.23 (s, 1H), 9.36 (s, 1H,). ^{13}C NMR (100 MHz, DMSO-d_6) 36.60 (CH_3), 19.0, 25.0, 30.1, 36.62, 61.4, 65.7, 69.3 (CH_2), 97.9 (CH), 118.2, 126.0, 127.7, 152.1 (CH_{arom}), 125.4, 135.1, 135.2, 135.7, 150.9 (C_{arom}). Mp: 84–86 °C. IR (ATR) 2943, 2869, 1685, 1586, 1452 cm^{-1}. HRMS (ESI+) calcd for $C_{18}H_{23}{}^{35}ClNO_5S$ (M+H)$^+$ 400.0980, found 400.0985.

2-[6-Chloro-7-(hydroxymethyl)isoquinolin-3-yl]ethyl methanesulfonate (**11**). To a solution of **10** (551 mg, 1.378 mmol) in acetone (7 mL) was added a 2 M aqueous HCl solution (3.45 mL, 6.89 mmol) at room temperature. The solution was stirred for 5 h at this temperature before evaporation of the solvent. A saturated aqueous $NaHCO_3$ solution was added to reach pH = 9. Product was extracted with EtOAc. Combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography using EtOAc/MeOH 100:0 to 98:2 yielding compound **11** (415 mg, 1.314 mmol, 95%) as a white solid. TLC R_f = 0.3 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) 3.11 (s, 3H), 3.28 (t, *J* 6.4 Hz, 2H), 4.66 (t, *J* 6.4 Hz, 2H), 4.72 (d, *J* 5.4 Hz, 2H), 5.66 (t, *J* 5.4 Hz, 1H), 7.72 (s, 1H), 8.06 (s, 1H), 8.23 (s, 1H), 9.35 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 36.61 (CH_3), 36.68, 60.5, 69.4 (CH_2), 118.1, 125.56, 126.1, 152.0 (CH_{arom}), 125.54, 134.6, 135.4, 139.0, 150.6 (C_{arom}). Mp: 70–72 °C. IR (ATR) 3584–2931, 2162, 1686, 1585, 1451 cm^{-1}. HRMS (ESI+) calcd for $C_{13}H_{15}^{35}ClNO_4S$ (M+H)$^+$ 316.0405, found 316.0411.

2-(6-Chloro-7-formylisoquinolin-3-yl)ethyl methanesulfonate (**12**). Using similar procedure as described for 3: **11** (411 mg, 1.302 mmol) and MnO_2 (565 mg, 6.508 mmol) were heated in $CHCl_3$ (20 mL) at reflux for 24 h. After filtration of the mixture over Celite® pad and washing with EtOAc the crude material was purified by flash chromatography using EtOAc/cyclohexane 8:2 yielding compound **12** (299 mg, 0.953 mmol, 73%) as a pale yellow powder. TLC R_f = 0.40 (EtOAc/cyclohexane 8:2). ^{1}H NMR (400 MHz, DMSO-d_6) 3.13 (s, 3H), 3.34 (t, *J* 6.4 Hz, 2H), 4.68 (t, *J* 6.4 Hz, 2H), 7.82 (s, 1H), 8.22 (s, 1H), 8.76 (s, 1H), 9.55 (s, 1H), 10.42 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 36.6 (CH_3), 36.9, 69.1 (CH_2), 118.2, 127.5, 132.6, 154.3 (CH_{arom}), 124.8, 130.7, 135.3, 138.5, 154.1 (C_{arom}), 189.5 (CO). Mp: 130-132 °C. IR (ATR) 2330, 1686, 1618, 1587, 1447, 1339 cm^{-1}. HRMS (ESI+) calcd for $C_{13}H_{13}^{35}ClNO_4S$ (M+H)$^+$ 314.0248, found 314.0239.

2-(6-Chloro-7-formyl-5-nitroisoquinolin-3-yl)ethyl methanesulfonate (**13**). To a solution of **12** (295 mg, 0.942 mmol) in 2.1 mL concentrated H_2SO_4 at room temperature was slowly added 65% HNO_3 solution (78 µL, 1.13 mmol). The reaction was heated at 50 °C overnight and finally poured on crushed ice/water. The solution was neutralized with portions of solid $NaHCO_3$ to reach pH = 9. Product was extracted with EtOAc and combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude material was purified by flash chromatography using CH_2Cl_2/EtOAc 9:1 to 8:2 yielding compound **13** (260 mg, 0.725 mmol, 77%) as a pale yellow powder. TLC: R_f = 0.4 (CH_2Cl_2/EtOAc 9:1). ^{1}H NMR (400 MHz, DMSO-d_6) 3.13 (s, 3H), 3.41 (t, *J* 6.4 Hz, 2H), 4.69 (t, *J* 6.4 Hz, 2H), 7.70 (s, 1H), 9.03 (s, 1H), 9.75 (s, 1H), 10.38 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 36.6 (CH_3), 36.8, 68.8 (CH_2), 112.1, 134.5, 154.8 (CH_{arom}), 124.6, 127.3, 129.6, 130.3, 145.1, 157.2 (C_{arom}), 187.9 (CHO). Mp: 142-143 °C. IR (ATR) 1693, 1615, 1534, 1325, 1168 cm^{-1}. HRMS (ESI+) calcd for $C_{13}H_{12}^{35}ClN_2O_6S$ (M+H)$^+$ 359.0099, found 359.0099.

10-Nitro-8-vinylpyrido[3,4-*g*]quinazolin-2-amine (**14**). Using standard procedure as described,[1] a CEM microwave tube was charged with **13** (193 mg, 0.538 mmol), guanidine carbonate (126 mg, 0.699 mmol) and DMF (4 mL, peptide synthesis grade). Argon was bubbled through the solution for 20 min. The tube was irradiated in a CEM microwave at 300 W for 45 s at 166 °C. Water was added and product was extracted with EtOAc (large volume). Combined organic phases were washed with water and saturated brine solution, dried over $MgSO_4$ and evaporated under reduced pressure. The crude material was purified by flash chromatography using EtOAc/cyclohexane 8:2 to 10:0 and finally EtOAc/MeOH 95:5 to 90:10 yielding compound **14** (95 mg, 0.355 mmol, 66%) as a brown powder. TLC R_f = 0.5 (EtOAc/cyclohexane 9:1). ^{1}H NMR (400 MHz, DMSO-d_6) 5.62 (dd, *J* 10.8 Hz, *J* 2 Hz, 1H), 6.51 (dd, *J* 16.8 Hz, *J* 2 Hz, 1H), 7.04 (dd, *J* 16.8 Hz, *J* 10.8 Hz, 1H), 7.46 (s, 1H), 7.95 (br s, 1H), 8.02 (br s, 1H), 8.95 (s, 1H), 9.51 (s, 1H), 9.55 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 119.2 ($CH_{2\ alkene}$), 109.9 (CH_{alkene}), 134.0, 136.2, 155.2, 165.7 (CH_{arom}), 120.4, 121.4, 129.3, 136.6, 142.1, 151.5, 161.3 (C_{arom}). Mp > 250 °C. IR (ATR) 3551-2698, 1666, 1612, 1574, 1503, 1288 cm^{-1}. HRMS (ESI+)

calcd for $C_{13}H_{10}N_5O_2$ (M+H)$^+$ 268.0829, found 268.0821.

5-[5-Chloro-2-formyl-4-(hydroxymethyl)phenyl]pent-4-ynenitrile (15). To a solution of A (700 mg, 2.36 mmol) in triethylamine (14 mL), under argon atmosphere, were successively added CuI (18 mg, 0.094 mmol), PdCl$_2$(PPh$_3$)$_2$ (33 mg, 0.047 mmol) and 4-pentynenitrile (530 µL, 5.902 mmol). The mixture was stirred at 50 °C for 3 h. The solvent was removed in vacuo and the crude material was purified by flash chromatography using EtOAc/cyclohexane (4:6 to 2:1) yielding compound 15 (543 mg, 2.20 mmol, 93%) as a white solid. TLC R$_f$ = 0.3 (EtOAc/cyclohexane 2:3). ^{1}H NMR (400 MHz, DMSO-d_6) 2.89 (t, *J* 2.5 Hz, 4H), 4.59 (d, *J* 5.5 Hz, 2H), 5.65 (t, *J* 5.7 Hz, 1H), 7.66 (s, 1H); 8.00 (s, 1H), 10.42 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 16.0, 16.4, 59.8 (CH$_2$), 76.5, 95.6 (C$_{alkyne}$), 119.7 (CN), 125.2, 134.3, 136.8, 141.2 (C$_{arom}$), 126.0, 132.9 (CH$_{arom}$), 190.7 (CO). Mp: 111 − 113 °C. IR (ATR) 3263, 3002 − 2782, 2250, 1684, 1598, 1395 cm^{-1}. HRMS (ESI+) calcd for $C_{13}H_{11}{}^{35}ClNO_2$ (M+H)$^+$ 248.0478, found 248.0473.

3-[6-Chloro-7-(hydroxymethyl)isoquinolin-3-yl]propanenitrile (16). Using the same procedure as described for 9: 15 (537 mg, 2.18 mmol), MeOH/NH$_3$ (5.8 mL). Flash chromatography using EtOAc/MeOH (100:0 to 98:2), yielding compound 16 (378 mg, 1.53 mmol, 70%) as a brown oil which was dissolved in a minimum of acetone and cyclohexane leading to a greenish solid after evaporation. TLC R$_f$ = 0.4 (EtOAc). ^{1}H NMR (400 MHz, DMSO-d_6) 2.99 (t, *J* 7.0 Hz, 2H), 3.17 (t, *J* 7.1 Hz, 2H), 4.72 (d, *J* 4.7 Hz, 2H), 5.68 (t, *J* 5.5 Hz, 1H), 7.73 (s, 1H), 8.07 (s, 1H), 8.24 (s, 1H), 9.36 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 16.2, 32.5, 60.5 (CH$_2$), 117.3, 125.57, 126.1, 152.1 (CH$_{arom}$), 120.3 (CN), 125.58, 134.6, 135.3, 138.9, 151.9 (C$_{arom}$). Mp: 114 − 116 °C. IR (ATR) 3305, 3088 − 2762, 2246, 1629, 1423 cm^{-1}. HRMS (ESI+) calcd for $C_{13}H_{12}{}^{35}ClN_2O$ (M+H)$^+$ 247.0638 ; found 247.0649.

3-(6-Chloro-7-formylisoquinolin-3-yl)propanenitrile (17). To a solution of 16 (635 mg, 2.57 mmol) in CHCl$_3$ (26 mL) was added MnO$_2$ (672 mg, 7.72 mmol). The mixture was stirred at reflux for 5 h, filtered through a pad of Celite® and washed with EtOAc. The filtrate was concentrated in vacuo. The crude material was triturated with cyclohexane and diisopropyl ether yielding compound 17 (571 mg, 2.33 mmol, 90%) as a white solid after filtration. TLC R$_f$ = 0.75 (EtOAc). RMN ^{1}H (400 MHz, DMSO-d_6) 3.02 (t, *J* 7.1 Hz, 2H), 3.23 (t, *J* 7.1 Hz, 2H), 7.83 (s, 1H), 8.23 (s, 1H), 8.77 (s, 1H), 9.56 (s, 1H), 10.43 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 16.0, 32.6 (CH$_2$), 117.6, 127.6, 132.5, 154.4 (CH$_{arom}$), 120.2 (CN), 124.8, 130.7, 135.4, 138.5, 155.2 (C$_{arom}$), 189.5 (CHO). Mp: 145 − 147 °C. IR (ATR) 3175 − 2845, 2241, 1750, 1560, 1447 cm^{-1} HRMS (ESI+) calcd for $C_{13}H_{10}{}^{35}ClN_2O$ (M+H)$^+$ 245.0482, found 245.0502.

3-(6-Chloro-7-formyl-5-nitroisoquinolin-3-yl)propanamide (18). To a solution of isoquinoline 17 (250 mg, 1.02 mmol) in H$_2$SO$_4$ (2.5 mL) was added portionwise KNO$_3$ (155 mg, 1.53 mmol) over 15 min. Additional KNO$_3$ (26 mg) was added after two days stirring at room temperature. Upon completion of the reaction (3 days, TLC control) the mixture was poured in a minimum of crushed ice/water and the aqueous solution was made alkaline by addition of solid NaHCO$_3$. The product was extracted several times with EtOAc. Organic layers were dried (MgSO$_4$) and concentrated under reduced pressure after filtration, yielding compound 18 (267 mg, 0.86 mmol, 85%) as a pale yellow solid. TLC R$_f$ = 0.4 (Acetone/CH$_2$Cl$_2$ 1:1). RMN ^{1}H (400 MHz, DMSO-d_6) 2.58 (t, *J* 7.5 Hz, 2H), 3.17 (t, *J* 7.5 Hz, 2H), 6.80 (br s, NH), 7.35 (br s, NH), 7.52 (s, 1H), 9.00 (s, 1H), 9.70 (s, 1H), 10.37 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 33.2, 34.0 (CH$_2$), 110.6, 134.4, 154.5 (CH$_{arom}$), 124.3, 127.1, 129.6, 129.9, 145.0, 161.4 (C$_{arom}$), 173.1, 187.9 (CO). Mp: 210-211 °C IR (ATR) 3524-2952, 1694, 1669, 1619, 1539, 1432, 1279 cm^{-1} HRMS (ESI+) calcd for $C_{13}H_{11}{}^{35}ClN_3O_4$ (M+H)$^+$ 308.0433, found 308.0432.

3-(2-Amino-10-nitropyrido[3,4-*g*]quinazolin-8-yl)propanamide (19). A suspension of compound 18 (50 mg, 0.16 mmol) and guanidine carbonate (40 mg, 0.22 mmol) in DMA (2 mL) was degassed with argon for 30 min then heated at 111 °C (oil bath) for a total time of 25 min. After completion of the reaction, EtOAc was added. The resulting slurry was filtered on a pad of Celite® and washed with EtOAc. The organic layer was washed

with water and brine, dried (MgSO$_4$) and the volatiles were removed under reduced pressure. The residue was purified by flash chromatography using CH$_2$Cl$_2$/MeOH (from 95:5 to 90:10), yielding tricyclic compound 19 (19 mg, 0.042 mmol, 26%) as a golden yellow solid. TLC R$_f$ = 0.3 (CH$_2$Cl$_2$/MeOH 95:5, eluted twice). ^{1}H NMR (400 MHz, DMSO-d_6) 2.56 (t, under solvent signal), 3.09 (t, *J* 7.5 Hz, 2H), 6.80 (br s, NH), 7.32 (s, 1H), 7.35 (br s, NH), 7.95 (br s, NH), 8.03 (br s, NH), 8.95 (s, 1H), 9.49 (s, 1H), 9.55 (s, 1H). ^{13}C NMR Not recorded due to low solubility. Mp > 285 °C. IR (ATR) 3420 − 3040, 1701, 1674, 1620, 1546, 1413 cm^{-1}. HRMS (ESI+) calcd for C$_{14}$H$_{13}$N$_6$O$_3$ (M+H)$^+$ 313.1044, found 313.1043. HPLC: purity > 96%, λ = 240 nm, t$_R$ = 4.7 min.

3-(2,10-Diaminopyrido[3,4-*g*]quinazolin-8-yl)propanamide (**20**). To a suspension of compound 19 (15 mg, 0.048 mmol) in 15 mL of anhydrous THF was added palladium on charcoal (10% wt, 3 mg, 0.003 mmol). The mixture was stirred under 7 bars of H$_2$ for 2 days, and filtered through Celite®. The Celite® pad was washed several times with EtOAc. Combined filtrates were concentrated under reduced pressure to give compound 20 as a red solid (10 mg, 0.035 mmol, 73%). TLC R$_f$ = 0.2 (CH$_2$Cl$_2$/MeOH 9:1). ^{1}H NMR (400 MHz, DMSO-d_6) 2.57 (t, *J* 7.8 Hz, 2H), 3.03 (t, *J* 7.8 Hz, 2H), 6.10 (br s, NH$_2$), 6.77 (br s, NH), 6.97 (br s, NH), 7.35 (br s, NH), 7.80 (s, 1H), 7.83 (s, 1H), 8.48 (br s, NH), 9.18 (s, 1H), 9.32 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6) 33.5, 34.9 (CH$_2$), 112.1, 113.9, 154.4, 164.8 (CH$_{arom}$), 118.6, 121.9, 123.2, 135.1, 135.3, 150.9, 158.6 (C$_{arom}$), 173.8 (CO). Mp: 235 °C (dec.). IR (ATR) 3529-2515, 1665, 1608, 1548, 1388 cm^{-1}. HRMS (ESI+) calcd for C$_{14}$H$_{15}$N$_6$O (M+H)$^+$ 283.1302 found 283.1296.

Acknowledgments

Supplementary Material

Copies of proton and carbon-13 NMR spectra of all newly synthesized molecules **4**-**20** are presented as supporting information in Supplementary Materials. Readers will be able to access this supporting information using the link "Supplementary Material" in the journal issue contents page.

References

1. Esvan, Y. J.; Zeinyeh, W.; Boibessot, T.; Nauton, L.; Théry, V.; Knapp, S.; Chaikuad, A.; Loaëc, N.; Meijer, L.; Anizon, F.; Giraud, F.; Moreau, P. *Eur. J. Med. Chem.* **2016**, *118*, 170-177.
   https://doi.org/10.1016/j.ejmech.2016.04.004
2. Zeinyeh, W.; Esvan, Y. J.; Nauton, L.; Loaëc, N.; Meijer, L.; Théry, V.; Anizon, F.; Giraud, F.; Moreau, P. *Bioorg. Med. Chem. Lett*. **2016**, *26*, 4327-4329.
   https://doi.org/10.1016/j.bmcl.2016.07.032

3. Zeinyeh, W.; Esvan, Y. J.; Josselin, B.; Baratte, B.; Bach, S.; Nauton, L.; Théry, V.; Ruchaud, S.; Anizon, F.; Giraud, F.; Moreau, P. *Bioorg. Med. Chem*. **2019**, *27*, 2083-2089.
    https://doi.org/10.1016/j.bmc.2019.04.005

4. Tazarki, H.; Zeinyeh, W.; Esvan, Y. J.; Knapp, S.; Chatterjee, D.; Schröder, M.; Joerger, A. C.; Khiari, J.; Josselin, B; Baratte, B.; Bach, S.; Ruchaud, S.; Anizon, F.; Giraud, F.; Moreau, P. *Eur. J. Med. Chem.* **2019**, *166*, 304-317.
    https://doi.org/10.1016/j.ejmech.2019.01.052

5. Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc*. **1987**, *109*, 2759-2770.
    https://doi.org/10.1021/ja00243a032

6. Dehnhardt C. M.; Megati, S.; Michalak, R. S.; Raveendranath, P. US20050070723, 2005; *Chem. Abstr*. **2005**, *142*, 355160.

7. Alfonsi, M.; Dell'Acqua, M.; Facoetti, D.; Arcadi, A.; Abbiati, G.; Rossi, E. *Eur. J. Org. Chem*. **2009**, 2852-2862.
    https://doi.org/10.1002/ejoc.200900014

8. Yoshida, Y.; Barrett, D.; Azami, H.; Morinaga, C.; Matsumoto, S.; Matsumoto, Y.; Takasugi, H. *Bioorg. Med. Chem*. **1999**, *7*, 2647-2666.
    https://doi.org/10.1016/S0968-0896(99)00203-5

9. Saito, Y.; Matsumoto, K.; Bag, S. S.; Ogasawara, S.; Fujimoto, K.; Hanawa, K.; Saito, I. *Tetrahedron* **2008**, *64*, 3578-3588.
    https://doi.org/10.1016/j.tet.2008.01.091

10. Bordwell, F. G.; Garbisch Jr., E. W. *J. Am. Chem. Soc*. **1960**, *82*, 3588-3598.
    https://doi.org/10.1021/ja01499a029

11. Zhou, Z.-L.; Kher, S. M.; Cai, S. X.; Whittemore, E. R.; Espitia, S. A.; Hawkinson, J. E.; Tran, M.; Woodward, R. M.; Weber, E.; Keana, J. F. W. *Bioorg. Med. Chem*. **2003**, *11*, 1769-1780.
    https://doi.org/10.1016/S0968-0896(03)00059-2

12. Nowrouzi, N.; Mehranpour, A. M.; Bashiri, E.; Shayan, Z. *Tetrahedron Lett*. **2012**, *53*, 4841-4842.
    https://doi.org/10.1016/j.tetlet.2012.06.126

13. Hajipour, A. R.; Ruoho, A. E. *Tetrahedron Lett*. **2005**, *46*, 8307-8310.
    https://doi.org/10.1016/j.tetlet.2005.09.178

14. Riego, J. M.; Sedin, Z.; Zaldívar, J. M.; Marziano, N. C.; Tortato, C. *Tetrahedron Lett*. **1996**, *37*, 513-516.
    https://doi.org/10.1016/0040-4039(95)02174-4

15. Shea, K. M.; Jaquinod, L.; Smith, K. M. *J. Org. Chem.* **1998**, *63*, 7013-7021.
    https://doi.org/10.1021/jo980965p

16. Smith, N. W.; Dzyuba, S. V. *Arkivoc* **2010**, *7*, 10-18.
    https://doi.org/10.3998/ark.5550190.0011.702

17. Štefane, B.; Požgan, F.; Sosič, I.; Gobec, S. *Tetrahedron Lett*. **2012**, *53*, 1964-1967.
    https://doi.org/10.1016/j.tetlet.2012.02.017

18. Bach, S.; Knockaert, M.; Reinhardt, J.; Lozach, O.; Schmitt, S.; Baratte, B.; Koken, M.; Coburn, S. P.; Tang, L.; Jiang, T.*;*Liang, D.-C.; Galons, H.; Dierick, J. F.; Pinna, L. A.; Meggio, F.; Totzke, F.; Schächtele, C.; Lerman, A. S.; Carnero, A.; Wan, Y.; Gray, N.; Meijer, L. *J. Biol. Chem.* **2005**, *280*, 31208-31219.
    https://doi.org/10.1074/jbc.M500806200